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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/683,055	10/29/98	JUNE	RPI-002CPBCN

HM12/1001

LAHIVE & COCKFIELD
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GAMBEL, EXAMINER

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 10/01/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 8/2/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1, 46, 47, 54-58, 69-72 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1, 46, 47, 54-58, 69-72 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The request filed 8/2/01 (Paper No. 16) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/183,055 is acceptable and a CPA has been established
An Office Action on the CPA follows.

Applicant's amendment, filed 8/2/01 (Paper No. 16), is acknowledged.
Claims 50-53 have been canceled. Claims 2-44, 45, 48, 49 and 59-68 have been canceled previously.
Claim 1 has been amended.

Claims 1, 46, 47, 54-58 and 69-72 are pending.

2. Applicant is reminded of the following.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, the CRF submission filed 10/12/99 fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures previously sent in Paper No. 11.

The following procedure is to be used for cases that contain the same sequence disclosure as the parent. The applicant need not submit a new computer readable from of the Sequence Listing in this continuation. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

Applicant is reminded to amend the specification and the claims accordingly, if necessary.

3. The drawings submitted with this application were declared informal by the applicant. Accordingly, they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review
The Brief Description of the Drawings should be amended to recite the different part numbers of the drawings (e.g. Figures 5A-C).

4. Applicant is reminded to amend the first line of the specification to update the status of priority documents

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

6. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. In addition, applicant should carefully review the application for other errors such as missing information (see page 35, line 7).

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant should carefully remove the specification for corrections

8. The instant methods do not receive priority back to USSN 07/275,433, filed 11/23/88, because USSN 07/275,433 does not appear to provide written support for "methods for including $CD8^+$ T cells within a population of T cells, comprising activating a population of T cells by contacting said population of T cells with an anti-CD3 antibody and stimulating an accessory molecule on the surface of the T cells with a ligand which binds the accessory molecule, the activating and stimulating steps thereby inducing proliferation of $CD8^+$T cells ".

If applicant desires priority back to USSN 07/275,433, filed 11/23/88; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Given the number of continuation-in-part priority applications, applicant is invited to indicate the particular priority application, upon which applicant is relying upon for earliest priority of the claimed invention / "limitations".

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1, 46, 47 and 56-58 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing a "ligand which binds the accessory molecule CD9" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of both the "ligand", are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

It does not appear that the specification as filed provides sufficient written description for a ligand other than CD9-specific antibodies that would provide the specificity and activity required by the claimed CD9-specific ligands in the claimed methods.

It does not appear that the specification as filed provides sufficient written description for the critical common structural attributes of a ligand other than CD9-specific antibodies.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species or a single species (anti-CD9 antibodies) to support an entire genus. The instant invention encompasses targeting CD9 with any ligand, yet the instant specification does not provide sufficient written description as to the structural features of said ligands and the correlation between the chemical structure and the function of the genus of ligands other than anti-CD9 antibodies. The reliance on the disclosed limited example of anti-CD9 antibodies does not support the written description of any ligand. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological and pharmacological activities. Therefore, structurally unrelated ligands other than anti-CD9 antibodies encompassed by the claimed invention would be expected to have greater differences in their structures, expression and activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a ligand, encompassed by the claimed invention. There is insufficient guidance based on the reliance of anti CD9 antibodies to direct a person of skill in the art to select or to predict particular sequences as essential for identifying any ligand, encompassed by the claimed invention. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

The instant claims do not provide functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of ligands, and because the genus is highly variable, anti-CD9 antibodies are insufficient to describe the genus of CD9-specific ligands encompassed by the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of ligands and CD9 ligands, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

11. Claims 1, 46, 47 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "anti-CD9 antibodies" as CD9-specific ligands, does not reasonably provide enablement for any "CD9-specific ligand" to be employed in the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies CD9-specific ligands other than those encompassed by "anti-CD9 antibodies" as disclosed in the specification as filed and set forth in claim 69 for example . CD9 ligand may have some notion of the activity of the receptor and ligand, claiming biochemical molecules by a particular name given to the protein (e.g receptor or ligand) by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any ligand for CD9.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any CD9-specific ligand, yet the instant specification does not provide sufficient guidance and direction as to the structural features of said CD9 ligands and the correlation between the chemical structure and the desired CD9 ligand. The reliance on the disclosed limited example of "anti-CD9 antibodies" does not support the enablement for any CD9 ligand.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species or a single species of anti-CD9 antibodies to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological and pharmacological properties. Therefore, structurally unrelated ligands encompassed by the claimed invention other than "anti-CD9 antibodies" would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence or a limited number of species and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Because of the lack of sufficient guidance and predictability in determining which structures would lead to CD9 ligands with the desired structural and functional properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the CD9-specific antibodies does not appear to provide sufficient enabling support for any ligand or CD9 and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using CD9 ligands would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

12. Claims 1, 46, 47, and 54-58 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 46, 47 and 54-58 are indefinite in they appear to be incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. For example, the claims lacks the activating and stimulating steps.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

13. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 46, 47, and 54-58 and 69-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 5,858,358 (June et al.) for the reasons of record.

Although the conflicting claims are not identical, the are not patentably distinct from each other because the instant claims, as they read on stimulating the proliferation of T cells, including $CD8^+$ T cells, appear to rely upon the same or nearly the same method steps and ingredients, particularly the use of CD3-specific and CD9-specific antibodies

17. No claim is allowed.

The instant claims appear to be free of the art, other than the obvious double patenting rejection set forth herein.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
October 1, 2001